IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	King, et al.
U.S. Serial No.	:	10/593,217, National Stage Application of International Application No. PCT/US2005/010152, filed March 25, 2005, claiming priority of U.S. Serial No.60/556,565, filed March 26, 2004
Filed	:	September 15, 2006
Confirmation No.:		7034
Examiner	:	Not Yet Known
Art Unit	:	Not Yet Known
For	:	COMBINATION THERAPY COMPRISING CLORETAZINE™

Law Offices of Albert Wai-Kit Chan, LLC
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April 30, 2007

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, Applicants would like to direct the Examiner's attention to the following references which are listed below and on Forms PTO/SB/08A and PTO/SB/08B (which are attached hereto as **Exhibit A**), and further attached as **Exhibits 1-20.**

Applicants would like to note that the listed references 1-14 are issued U.S. Patents and/or U.S. Publications. In addition, reference number 17 was cited by the examiner in related U.S. Patent No.

6,855,695, issued February 15, 2005. Accordingly, pursuant to 37 CFR 1.98(d), a copy of these references is not required to be submitted with this SIDS. However, Applicants invites the Examiner to contact the Applicants' undersigned attorney's office if a copy of any of the listed references is desired.

1. U.S. Patent No. 4,175,200 November 20, 1979, Hunter, et al., "N, N-Disubstituted Sulfonyl Hydrazines"

2. U.S. Patent No. 4,385,055, May 24, 1983, Klayman, et al., "2-ACetyl-And 2-Propionylpyridine Thiosemicarbazones as Antimalarials"

3. U.S. Patent No. 4,447,427, May 8, 1984, Klayman, et al., "2-ACetyl-And 2-Propionylpyridine Thiosemicarbazones"

4. U.S. Patent No. 4,684,747, August 4, 1987, Satorelli, et al., "N, N'-bis(sulfonyl)hydrazines Having Antineoplastic Activity"

5. U.S. Patent No. 4,696,938, September 29, 1987, Satorelli, Le, Dat P., "Insecticidal 6-aryl-pyridine Thiosemicarbazones"

6. U.S. Patent No. 4,849,563, July 18, 1989, Satorelli, et al., "Novel 1-alkyl-1-arenesulfonyl-2-alkoxycabonylsulfenyl hydrazines Having Antineoplascti Activity"

7. U.S. Patent No. 5,101,072, March 31, 1992, Satorelli, et al., "Sulfonylhydrazines and Their Uses as Antineoplastic Agents and as Antitrypanosomal Agents"

8. U.S. Patent No. 5,214,068, May 25, 1993, Satorelli, et al., "Sulfonylhydrazines and Their Uses as Antineoplastic Agents and as Antitrypanosomal Agents"

9. U.S. Patent No. 5,256,820, October 26, 1993, Satorelli, et al., "1-alkyl-2-acyl-1, 2-disulfonylhydrazines"

10. U.S. Patent No. 5,637,619, June 10, 1997, Satorelli, et al., "Antitumor 2-aminocarbonyl-1, 2-bis(methylsulfonyl)-1-(substituted)hydrazines"

11. U.S. Patent No. 5,767,134, June, 16, 1998, Li, et al., "Prodrug Forms of Ribonucleotide Reductase Inhibitors 3-AP and 3-AMP"

12. U.S. Patent No. 6,040,338, March 21, 2000, Satorelli, et al., "N, n-bis(sulfonyl)hydrazines Useful as Antineoplastic Agents"

13. U.S. Patent No. 6,696,487, February 24, 2004, Gerusz, et al., "Fungicidal Phenyl (thio) Urea and Phenyl (thio) Cabamate Derivatives"

14. U.S. Patent No. 6,855,695, February 15, 2005, Xu, et al., "Water-Soluble Shps as Novel Alkylating Agents"

15. International Publication No. WO/2002/030424, April 18, 2002, Doyle, et al., "Modified Prodrug Forms of Ap/Amp" **[Exhibit 1]**

16. Baumann RP, et al., 2004, "1,2-Bis(methylsulfonyl)-1-(2-chloroethyl)-2-[(methylamino)carbonyl]hydrazine (VNP40101M): II. Role of O6-alkylguanine-DNA alkyltransferase in

cytotoxicity." Cancer Chemother Pharmacol. 53(4):288-295 **[Exhibit 2]**

17. Burchenal, et al., 1988, "Cancer: the Outlaw Cell," ed. Richard E Lafond, American Chemical Society: 204-205

18. Gura, et al., 1997, "Systems for identifying new drugs are often faulty," Science: 278(5340):1041-2 **[Exhibit 3]**

19. Lee, et al., 2002, "Toxicological evaluation of 1,2 bis("methylsulfonyl)-1-(2-chloroethyl)-2(methylaminocarbonyl) hydrazine (VNP40101M), novel alkylating Agent with Potential Antitumor Activity, with Intravenous Administration in Rats and Dogs", International Journal of Toxicology. Vol. 23: 23-39 **[Exhibit 4]**

20. Hrubiec, et al., 1986, "Synthesis and evaluation of 1-(arylsulfonyl)-2-[(methoxycarbonyl)sulfenyl]-1 methylhydrazines ++ + as antineoplastic agents." J Med Chem. 29(9):1777-9 **[Exhibit 5]**

21. Hrubiec, et al., 1986, "Synthesis and evaluation of 2-substituted 1-methyl-1-(4-tolylsulfonyl)hydrazines as antineoplastic agents," J Med Chem. 29(7):1299-301 **[Exhibit 6]**

22. Murren, et al., 2005, "A phase I and pharmacokinetic study of VNP40101M, a new alkylating agent, in patients with advanced or metastatic cancer", Investigational New Drugs. Vol 23: 123-135 **[Exhibit 7]**

23. Mao, et al., 2002, "Pharmacokinetics, Mass Balance, and Tissue Distribution of a Novel DNA Alkylating Agent, VNP40101M, in Rats", AAPS PharmSci: 4(4)24 **[Exhibit 8]**

24. Penketh, et al., 1994, "Studies on the mechanism of decomposition and structural factors affecting the aqueous stability of 1,2-bis(sulfonyl)-1-alkylhydrazines", J Med Chem 37: 2912-2917 **[Exhibit 9]**

25. Penketh, et al., 2000, "Comparison of DNA lesions produced by tumor-inhibitory 1,2-bis(sulfonyl)hydrazines and chloroethylnitrosoureas", Biochem Pharmacol 59:283-91 **[Exhibit 10]**

26. Pratviel, et al., 1989, "Cytotoxic and DNA-damaging Effects of 1,2-bis(sulfonyl)hydrazines on Human Cells of the Mer+ and Mer- phenotype", Cancer Biochem Biophys 10:365-75 (abstract only) **[Exhibit 11]**

27. Shyam, et al., 1985, "Synthesis and evaluation of N,N'-bis(arylsulfonyl)hydrazines as antineoplastic agents" J Med Chem 28:525-7 **[Exhibit 12]**

28. Shyam, et al., 1986, "1,2-bis(arylsulfonyl)hydrazines. 2. The influence of arylsulfonyl and aralkylsulfonyl substituents on antitumor and alkylating activity", J Med Chem 29:1323-5 **[Exhibit 13]**

29. Shyam, et al., 1987, "1,2-Bis(sulfonyl)hydrazines. 3. Effects of structural modification on antineoplastic activity", J Med Chem 30:2157-61 **[Exhibit 14]**

30. Shyam, et al., 1990, "Synthesis and evaluation of 1,2,2-tris(sulfonyl)hydrazines as antineoplastic and trypanocidal agents", J Med Chem. 33(8):2259-64 **[Exhibit 15]**

31. Shyam, et al., 1993, "Synthesis and evaluation of 1-acyl-1,2-bis(methylsulfonyl)-2-(2- chloroethyl)hydrazines as antineoplastic agents", J Med Chem 36:3496-502 **[Exhibit 16]**

32. Shyam, et al., 1996, Antitumor 2-(aminocarbonyl)-1,2-bis(methylsulfonyl)-1-(2-chloroethyl)- hydrazines", J Med Chem 39:796-801 **[Exhibit 17]**

33. Giles, et al., 2004, "A Phase I and Pharmacokinetic Study of VNP40101M, a Novel Sulfonylhydrazine Alkylating Agent, in Patients with Refractory Leukemia.", Clinical Cancer Research, Vol. 10, Pages 2908-2917 **[Exhibit 18]**

34. Ishiguro, et al., 2005, "Role of 0-alkylguanine-DNA alkyltransferase in the cytotoxic activity of clorezatine", Mol Cancer Ther, Vol. 4 (11), Pages 1755-1763 **[Exhibit 19]**

35. Rice, et al., 2005, "Differential inhibition of cellular glutathione reductase activity by isocyanates generated from the antitumor prodrugs Cloretazine and BCNU." , Biochemical Pharmacology, Vol. 69, Pages 1463-1472 **[Exhibit 20]**

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Supplemental Information Disclosure Statement. However, if additional fees are required, authorization is given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

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Exhibit A

PTO/SB/08A (04-03)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	10/593,217
Filing Date	September 15, 2006
First Named Inventor	KING, et al.
Art Unit	Not Yet Known
Examiner Name	Not Yet Known
Attorney Docket Number	891-A-PCT-US

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US- 4,175,200	11-20-1979	Hunter, et al.	
	2	US- 4,385,055	05-24-1983	Klayman, et al.	
	3	US- 4,447,427	05-08-1984	Klayman, et al.	
	4	US- 4,684,747	08-04-1987	Satorelli, et al.	
	5	US- 4,696,938	09-29-1987	Satorelli, et al.	
	6	US- 4,849,563	07-18-1989	Satorelli, et al.	
	7	US- 5,101,072	03-31-1992	Satorelli, et al.	
	8	US- 5,214,068	05-25-1993	Satorelli, et al.	
	9	US- 5,256,820	10-26-1993	Satorelli, et al.	
	10	US- 5,637,619	06-10-1997	Satorelli, et al.	
	11	US- 5,767,134	06-16-1998	Li, et al.	
	12	US- 6,040,338	03-21-2000	Satorelli, et al.	
	13	US- 6,696,487	02-24-2004	Gerusz, et al.	
	14	US- 6,855,695	02-15-2005	Xu, et al.	
		US-			
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		US-			

FOREIGN PATENT DOCUMENTS

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	15	WO/2002/030424	04-18-2002	Doyle, et al.		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, Washington, DC 20231.**

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OTHER PRIOR ART–NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	16	Baumann RP, et al., 2004, "1,2-Bis(methylsulfonyl)-1-(2-chloroethyl)-2-[(methylamino)carbonyl]hydrazine (VNP40101M): II. Role of O6-alkylguanine-DNA alkyltransferase in cytotoxicity." Cancer Chemother Pharmacol. 53(4):288-295	
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	22	Murren, et al., 2005, "A phase I and pharmacokinetic study of VNP40101M, a new alkylating agent, in patients with advanced or metastatic cancer", Investigational New Drugs. Vol 23: 123-135	
	23	Mao, et al., 2002, "Pharmacokinetics, Mass Balance, and Tissue Distribution of a Novel DNA Alkylating Agent, VNP40101M, in Rats", AAPS PharmSci: 4(4)24	
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1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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Sheet 3 of 3

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OTHER PRIOR ART–NON PATENT LITERATURE DOCUMENTS

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	26	Pratviel, et al., 1989, "Cytotoxic and DNA-damaging Effects of 1,2-bis(sulfonyl)hydrazines on Human Cells of the Mer+ and Mer- phenotype", Cancer Biochem Biophys 10:365-75 (abstract only)	
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	31	Shyam, et al., 1993, "Synthesis and evaluation of 1-acyl-1,2-bis(methylsulfonyl)-2-(2- chloroethyl)hydrazines as antineoplastic agents", J Med Chem 36:3496-502	
	32	Shyam, et al., 1996, Antitumor 2-(aminocarbonyl)-1,2-bis(methylsulfonyl)-1-(2-chloroethyl)- hydrazines", J Med Chem 39:796-801	
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